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Feature Article

Type 2 Diabetes, Cardiovascular Disease, and the Evolutionary Paradox of the Polycystic Ovary Syndrome: A Fertility First Hypothesis

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ABSTRACT Worldwide, the high prevalence of the Polycystic Ovary Syndrome (PCOS), a heritable cause of ovarian infertility, is an evolutionary paradox, which provides insight into the susceptibility of well-fed human populations to cardiovascular disease and diabetes. We propose that PCOS, Type 2 diabetes (T2D) and the Metabolic Syndrome are modern phenotypic expressions of a metabolic genotype attuned to the dietary and energetic conditions of the Pleistocene. This metabolic "Fertility First" rather than "Thrifty" genotype persisted at high prevalence throughout the entire agrarian period—from around 12,000 years ago until 1800 AD—primarily, we contend, because it conferred a fertility advantage in an environment defined by chronic and often severe seasonal food shortage. Conversely, we argue that genetic adaptations to a high carbohydrate, low protein agrarian diet, with increased sensitivity to insulin action, were constrained because these adaptations compromised fertility by raising the lower bound of body weight and energy intake optimal for ovulation and reproduction. After 1800, the progressive attainment of dietary energy sufficiency released human populations from this constraint. This release, through the powerful mechanism of fertility selection, increased, in decades rather than centuries, the prevalence of a genotype better suited to carbohydrate metabolism. This putative mechanism for rapid and recent human evolution can explain the lower susceptibility to T2D of today's Europid populations. This hypothesis predicts that the increasing rates of diabetes and cardiovascular disease, which typically accompany economic development, will be tempered by natural, but particularly fertility, selection against the conserved ancestral genotypes that currently underpin them. Am. J. Hum. Biol. 21:587–598, 2009.

Evolutionary fitness is defined in terms of lifetime reproductive success, which in turn depends on survival and bodily maintenance until and during the reproductive years (Perlman, 2008). When average environmental conditions change, the mechanisms that balance the allocation of finite resources to growth, bodily maintenance, and reproduction may themselves be subject to natural selection (Burks et al., 2000; Holliday, 1989).

Since the beginning of the Holocene epoch modern humans have experienced two major shifts in average dietary and energetic conditions. The first was the transition from foraging and hunting to plant and especially grain cultivation, and animal breeding, which began in the Fertile Crescent 12,000 years ago, and subsequently developed independently in Africa, China, South East Asia, Papua New Guinea and Meso-America (Cavalli-Sforza et al., 1994). The second shift was the sustained improvements in nutrition and in the security of the food supply, which began in Europe in the eighteenth century. This "escape from hunger" (Fogel, 2004) has now extended to over two-thirds of humanity, but one-eighth of the world's population—nearly one billion people (FAO, 2008)—remain chronically hungry.

We present here an account of the impacts these shifts in average conditions have had on the recent coevolution of energy homeostasis and fertility in human populations, an account that we believe provides new perspectives into the origins, epidemiology, and future trajectory of the global epidemics of Type 2 diabetes (T2D) and the Metabolic Syndrome (MetS). The key scientific insight comes from an examination of the evolutionary paradox of the high prevalence of the Polycystic Ovary Syndrome (PCOS). This genetically based condition is globally the most common cause of anovulatory infertility (Homburg, 2003) and is strongly linked to both T2D and MetS. The prevalence of PCOS is around 10% in developed countries (Broekmans et al., 2006), although this clinical syndrome sits atop a spectrum of disordered polycystic ovarian morphology and function with an estimated prevalence of 20–30% in developed countries (Balen and Michelmore, 2002) including up to 52% of South Asian immigrant women in Britain (Rodin et al., 1998).

We argue, in essence:

1. That these three common conditions, each strongly associated with abdominal obesity, insulin resistance in muscle, and pancreatic β cell dysfunction, represent a persistence in modern populations of a metabolic genotype attuned to the energetic and dietary conditions of the Pleistocene era. During this period humans were hunter gatherers and had a substantially meat-based, high protein, low carbohydrate diet characterized by resistance to the action of insulin and a greater dependency on hepatic gluconeogenesis as the source of glucose for brain and reproductive function (Brand Miller

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and Colagiuri, 1994). These populations also conformed to norms for body size and fertility, which optimized, respectively, personal and lineage survival under these conditions (Vitzthum, 2001).

2. That the slow transition to agriculture, which ultimately inverted the proportion of carbohydrate to protein in the human diet, favored the emergence of genotypes with an increased sensitivity to insulin action—enabling the utilization of carbohydrates and sugars, rather than protein and fat as metabolic fuel (Brand Miller and Colagiuri, 1994; McMichael, 2001).
3. An additional consequence of this adaptation, we will argue, was a right shift in the U-shaped relationship between body weight and fertility, effectively raising the lower boundary of energy intake which was optimal for successful reproduction and particularly for the maintenance of ovulation (Speakman, 2007; Vitzthum, 2001). When combined with the generally poorer nutrition and health, and often severe seasonal food shortage of agricultural populations, this requirement, we contend, effectively constrained adaptation to a genotype better suited to carbohydrate metabolism throughout the entire agrarian period until about 1800 (Fogel, 2004; Wrigley and Schofield, 1981).
4. Conversely the insulin resistance associated with the Pleistocene Metabolic profile was, under the same meagre nutritional conditions, better able to divert available dietary energy to the maintenance of ovarian fertility and reproduction in times of hunger, and was preserved. Accordingly throughout this paper we have referred to this ancestral genotype as a "Fertility First"(rather than a Thrifty) genotype as we believe this better describes, in evolutionary terms, the means of its preservation.
5. The improvements in food distribution and agriculture, which began in Europe in the seventeenth and eighteenth centuries and which brought for the first time food security to a large proportion of the population, has progressively released humans from this adaptive constraint and has precipitated a rapid increase, within decades rather than centuries, in a genotype better suited to carbohydrate metabolism.
6. This increase, we argue, has been achieved through a mechanism of fertility selection; as caloric intake and body weight increased, selection for the "Fertility First" genotype reversed direction as an increasing proportion of women expressed the fertility inhibiting PCOS phenotype. In parallel, selection for the agrarian genotype increased as under-nutrition related infertility declined. Fertility selection is, in theory, capable of selection differentials between genotypes of 95% per generation—this would be equivalent to a nine-fold increase in the maximum observed selection differential between two alleles in human populations (e.g., those with and without a particular hemoglobinopathy in a malaria-prone area) due to survival or viability selection (Cavalli-Sforza et al., 1994; Fisher, 1930). This rapid and recent evolution is made more plausible by the accompanying context of unprecedented and rapid environmental change—the "escape from hunger", with its profound effects on human population growth, stature, mortality and fertility.
7. This hypothesis gives grounds for optimism that the modern epidemics of diabetes and cardiovascular disease in developing countries may be tempered in coming decades by rapid natural, but particularly fertility, selection against the conserved ancestral genotypes that currently underpin them.

HUMAN NUTRITION FROM THE PLEISTOCENE TO THE PRESENT

The fossil record suggests that in the cool and dry Pleistocene epoch, beginning about two million years ago, the hominid diet changed progressively from being predominantly vegetarian to one based largely on meat and animal products (Cordain, 2007; McMichael, 2001). The development of an enlarging and metabolically expensive brain was probably enabled by a reduction in gut size (Aiello and Wheeler, 1995), occurring in response to a shift towards a high quality meat based diet to provide the energy, amino acids, micronutrients and polyunsaturated fatty acids needed to meet these metabolic demands (Mann, 2000). Evidence from contemporary foraging populations suggests that this way of life demands a caloric intake in excess of 3,000 kcal/day (Eaton et al., 1997).

The archaeological evidence indicates a gradual shift, beginning around 12,000 years ago, from the consumption of root plants, wild pulses, various nuts and fruit and of hoofed mammals (gazelle, antelope and deer) to cultivated wheat and barley and domesticated sheep, goats, cattle, and pigs (Larsen, 2000). Driven variously by population increase, megafaunal extinction and climatic change, agriculture emerged independently over five millennia in five continents (Cavalli-Sforza et al., 1994; Flannery, 1994). Over this period there emerged a mosaic of food economies—foragers, primitive agriculturalists, pastoral nomads and later complex agricultural systems—living inter-dependently in all parts of the globe.

The paleodemography and paleopathology of early agrarians indicate that they had a poorer and less varied diet and poorer health than their hunter-gatherer forebears: a lower mean age at death, reduced stature and increased susceptibility to infectious disease (Cohen and Armelagos, 1984).

In almost all pre-industrial agrarian societies, chronic food shortage was ubiquitous and it was this, not famine (Fogel, 2004), that limited population growth (Wrigley and Schofield, 1981). Average daily calories per capita in England and France fell short of 2,400 kcal/day, the current FAO recommended minimum energy intake, until 1850 (Fogel, 2004). The energy intake of the typical diet in France in the eighteenth century was equivalent to that in present day Ethiopia, and in England in 1850 to that of rural India today (Fogel, 2004).

Beginning in Europe in the eighteenth century improvements in agriculture, transport and food distribution unshackled cycles of mortality and fertility from the price of grain (Fogel, 2004; Wrigley and Schofield, 1981). Improved nutrition followed gradually in nineteenth-century Europe, but increased rapidly and on a global scale after World War II, with a 25% increase—550 calories per capita—between 1961 and 2003. While these increases have reduced the prevalence of chronic energy deficiency (CED) [defined as a body mass index (BMI) less than 18.5 kg/m^2] to less than 5% in developed countries, the prevalence is still 10–25% in Sub-Saharan Africa, 9% in China, and 31% in India (WHO, 2009). These same increases

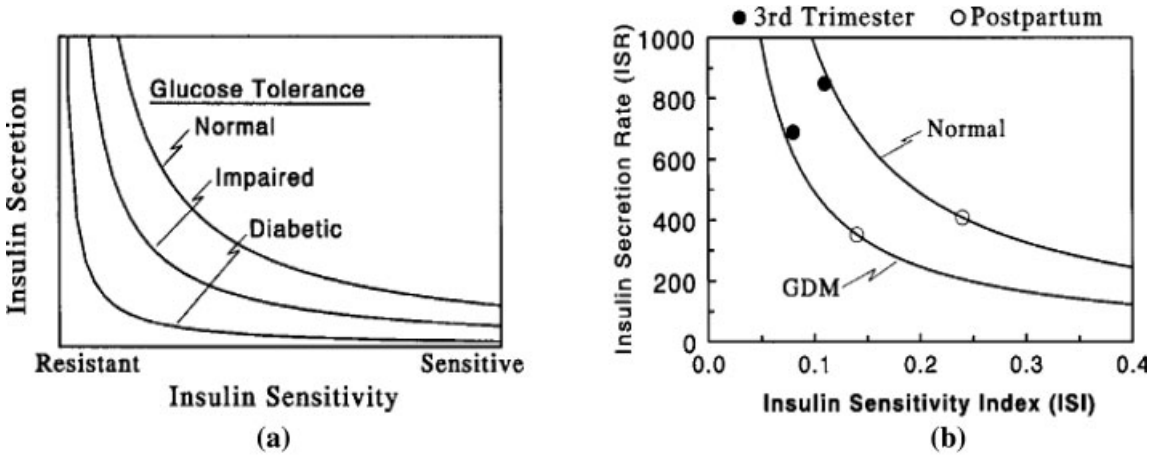

Fig. 1. (a) Schematic representation of hyperbolic relationships between insulin sensitivity and insulin secretion in groups with different blood glucose levels. Impaired includes PCOS, Gestational Diabetes Mellitus (GDM) and first degree relatives of those with T2D. (b) Insulin sensitivity-secretion relationships in women with GDM and normal women during the third trimester and post partum i.e. remote from pregnancy. In normal women, increases in insulin secretion are commensurate with the increases in insulin resistance of pregnancy. (Reprinted with permission from Buchanan, J Clin Endocrinol Metab, 2001, 86, 989–993, © Endocrine Society.)

have also led to unprecedented levels of obesity in children and adults in both developed and developing countries. Between 1961 and 1999, and against a background of declining per capita energy expenditure, the number of countries consuming a per capita calorie intake greater than 3,200 calories per day increased from 7 to 31 and the number of people from 110 million to 1 billion (Schmidhuber and Shetty, 2004). The rapidity of these changes has resulted in a dual burden of malnutrition in developing countries in which under nutrition and over nutrition co-exist in the same communities and even in the same family (Hawkes et al., 2004).

THE PLEISTOCENE INHERITANCE AND METABOLIC ADAPTATIONS TO THE AGRARIAN DIET

Physiological adaptations to the largely animal based diets during the Pleistocene—what the Canadian author Ronald Wright has called an "all-you-can kill barbeque" (Wright, 2004)—and the associated reduction in intake of plant sugars and lower glucose uptake resemble those seen in obligate carnivores such as felids (MacDonald et al., 1984) or raptors (Myers and Klasing, 1999). They include a limited ability to synthesize 20 and 22 carbon fatty acids, essential amino acids such as taurine (Cordain, 2007) and importantly a lower requirement for insulin, greater resistance to insulin action in muscle (Cordain, 2007; Reaven, 1998) and a higher dependence on hepatic gluconeogenesis as a source of glucose for brain and reproductive function (Brand Miller and Colagiuri, 1994).

Notwithstanding the brevity, in evolutionary terms, of time elapsed since the beginnings of agriculture, we contend that specific genetic adaptations to a higher carbohydrate, lower protein agrarian diet are also likely; and furthermore that some of the most important aspects of these adaptations can be inferred both from the epidemiology of the unfolding global epidemic of T2D, and the comparative physiology of people with and without this condition.

Although T2D has been traditionally understood as a metabolic disorder characterized by insulin resistance—the Pleistocene legacy common to PCOS, T2D and MetS—it now appears that insulin secretion, which is bound in a curvilinear relationship with insulin resistance by "open" or "closed" loop controls (Bergman et al., 2002), may have a primary role in each of these conditions (Bergman et al., 2002; Dunaif and Finegood, 1996; Florez, 2008; Porte, 1999). The trajectory of this curvilinear or hyperbolic relationship varies in those people with normal, impaired or overt glucose intolerance (Fig. 1a). Over a wide range of energy intake this Pleistocene metabolic profile is associated with higher levels of insulin, glucose and insulin resistance (Stumvoll et al., 2003).

Insulin is a phylogenetically ancient hormone, which in addition to regulating glucose and fatty acid metabolism influences growth and body weight, renal excretion of sodium and nitrogen, and fertility (Burks et al., 2000; Poretsky et al., 1999). The MetS is a constellation of major risk factors for cardiovascular disease—insulin resistance, hypertension, dyslipidemia and visceral adiposity, which in some populations may account for up to 60% of coronary heart disease (McKeigue et al., 1993). In particular, insulin resistance and hyperinsulinaemia are causally related to hypertension through direct effects on vascular tone, stimulation of the adrenergic nervous system, and antinatriuresis (Natali and Ferrannini, 2004). β-Cell impairment may also contribute to the deposition of intra-abdominal fat (Porte, 1999).

What is perceived as β cell impairment in these pathological states can more helpfully be viewed as a reduced plasticity of pancreatic β cell function in response to increasing demand (Buchanan et al., 1990; Del Prato et al., 2004). Indeed a robust plasticity of pancreatic β cell function in response to the increases in insulin resistance in pregnancy and obesity is both a hallmark of glucose regulation of people *without* these conditions (Buchanan and Xiang, 2005) and a plausible adaptation to a high carbohydrate diet (Fig. 1b).

Some support for the view that important adaptations during the agrarian era involved genes coding for pancreatic β cell growth and differentiation comes from initial analyses of recent positive selection in the human genome (The International HapMap Consortium, 2005; Voight

et al., 2006). In Europeans, the strongest signal for selection on recent mutations occurred near NKX2.2 gene, a member of the NK2 family of homeoprotein transcription factors, which regulates the differentiation of pancreatic endocrine cells (Sussel et al., 1998). Although the actual genetic target is uncertain, this mutation is very recent and is likely to have occurred during the agrarian era.

ENERGY HOMEOSTASIS, BODY WEIGHT, AND OVULATION

Fertility in a population is determined, first, by its fecundity, which sets an upper limit to reproductive capacity, and then by a number of fertility-inhibiting behavioral factors such as delayed marriage, contraception, and abortion and breastfeeding practices, which reduce fertility to a fraction of its potential (Bongaarts, 1980a).

Reproduction in women requires much greater energy expenditure than in men, and is very sensitive to the nutritional environment. Famines in the Netherlands in 1944 (Stein et al., 1975) and Bangladesh in 1974 (Bongaarts, 1980a; Mosley, 1979) dramatically reduced the birth rate. Women with anorexia nervosa also suffer severe weight loss and frequently cease to menstruate (Frisch, 2000). Chronic undernutrition can affect fertility by delaying menarche, reducing the age at menopause, prolonging the inhibition of ovulation with breastfeeding, reducing the frequency of ovulatory menstrual cycles and the quality and quantity of sperm, and increasing the probability of death in utero (Bongaarts, 1980b).

Ovarian function is exquisitely sensitive to nutritional status, showing a graded response to calorie reduction, with progression from initial suppression of the luteal and then follicular phase of the ovulatory cycle, to anovulation and reduced menstrual frequency (Ellison, 1990; Frisch, 2000).

Both hunter-foraging and horticultural societies suffer from seasonal fluctuations in food resources although the more varied diet of the former may protect them from energetic and fertility constraints (Bentley et al., 2001); In Lese horticulturists in the Ituri forest of the Congo, weight loss in the pre-harvest season is nearly universal. During that time these women have lower levels of salivary progesterone and estradiol, longer intermenstrual intervals and shorter durations of menstrual bleeding. These trends are reversed after the harvest. Efe pygmies, who are nomadic hunters and foragers, live alongside the Lese and supplement their diet with wild game and plants. The Efe, although exposed to similar environmental conditions, do not demonstrate either seasonal patterns of weight loss or births (Ellison, 1990).

The seasonal variation in ovarian function in agrarian populations is reflected in seasonal patterns of conception (Prentice et al., 2005) (see Fig. 2). This cyclical pattern of fertility is likely to have been the norm in many agrarian populations before 1800.

Metabolic signaling of undernutrition and ovulation

Frisch (2000) proposed that a minimum percentage of body fat was necessary to initiate menarche and sustain menstruation. A more recent consensus concludes that the availability of oxidisable metabolic fuel, rather than a minimum amount of fat, is the critical factor in maintaining ovarian function (ESHRE Capri Workshop Group, 2006; Wade and Jones, 2004).

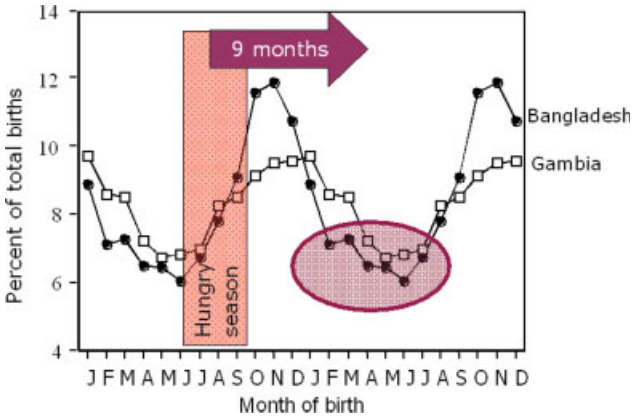

Fig. 2. Seasonal variations in fertility in Bangladesh and Gambia. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

Insulin, leptin (produced by adipose tissue), and blood glucose are important mediators of the relationship between energy balance and ovarian function (ESHRE Capri Workshop Group, 2006). The levels of all three fall during periods of starvation, but return to normal if energy balance is restored, albeit at a lower body weight and energy intake (Schwartz and Seeley, 1997). Plasma leptin and plasma insulin provide different information to the central nervous system about the amount and site of fat storage, respectively (Schwartz et al., 1997). Leptin secretion appears to be related to total adipose mass, whereas insulin secretion seems to be inversely related to insulin sensitivity, which reflects storage of triglycerides in visceral or abdominal adipose tissue and insulin resistance in muscle (Porte, 2006). Insulin is essential for fertility, stimulating production of luteinising hormone and increasing ovarian production of steroid hormones (Poretsky et al., 1999).

Leptin contributes to regulation of appetite and energy expenditure and influences the secretion of reproductive hormones. It has emerged as a key hormonal mediator of the adaptation to undernutrition and starvation, regulating neuroendocrinal responses to low energy intake (Chan and Mantzoros, 2006). Administration of leptin restores menstruation in women whose menstrual cycles have stopped because of low weight or excessive exercise (Welt et al., 2004). Leptin may act as a metabolic gate to gonadotrophin secretion, and observational studies suggest a critical threshold for blood leptin concentration to sustain ovulation is 2 μg/l (Holtkamp et al., 2003). Accordingly, genetic adaptations, which sustain levels of metabolic fuel and leptin if food is scarce, have the potential to optimize fecundity and fertility under these conditions. Our hypothesized Fertility First genotype, which is able to better sustain blood glucose under low energy conditions and preferentially deposits intra-abdominal fat, appears to have that potential.

Nutrition, body weight, and ovulatory infertility in human populations

Body weight has a strong influence on fertility in human populations. Both chronic undernutrition and

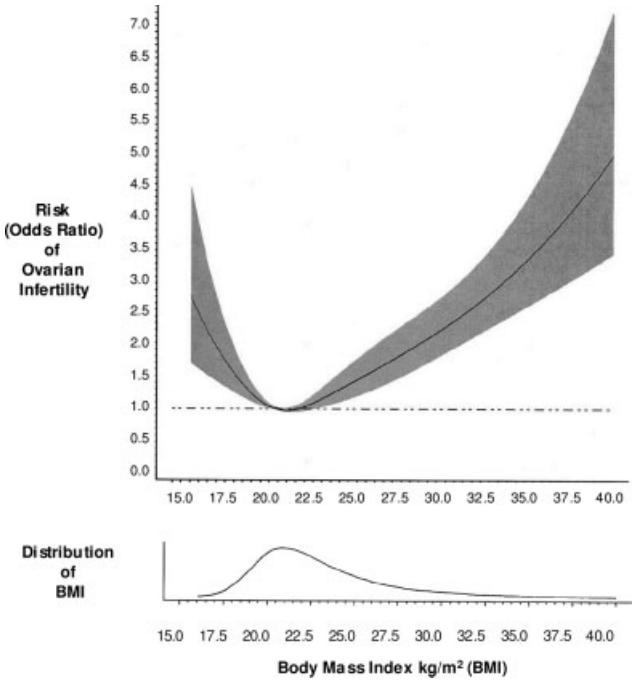

Fig. 3. Multivariate Odds Ratio and 95% Confidence Interval of ovulatory disorder infertility by body mass index and distribution of body mass index Nurses Health Study II, 1989–1995. The reference BMI is 21 kg/m^2 (Rich-Edwards et al., 2002).

overnutrition reduce ovarian fertility, with declines in fertility seen in both thin and obese women. The US-based Nurses Health Study II reported a U-shaped association between BMI and ovarian infertility, with an increased risk for BMI below 20.0 or above 24.0 kg/m^2 (Rich-Edwards et al., 2002) (Fig. 3, top graph). Given the BMI distribution of US women, 12% of ovulatory infertility is attributable to underweight (BMI $<$ 20.0) and 25% to overweight (BMI $>$ 25.0). Intriguingly, this U-shaped relationship between BMI and infertility is a mirror-image of the distribution of relative weight in the source population (Fig. 3, bottom graph). This suggests an underlying biological capacity for a population to optimize reproductive success in relation to prevailing dietary conditions.

POLYCYSTIC OVARY SYNDROME

The syndrome is diagnosed in women with at least two of the following three features: polycystic ovaries (PCO), excessive secretion of androgenic hormones and anovulatory menstrual cycles (The Rotterdam ESHRE/ASRM PCOS consensus, 2004). This broader consensual definition of PCOS, particularly the inclusion of the PCO-anovulation pairing with its lower association with metabolic abnormalities, yields a prevalence of PCOS of around 10% in developed countries (Broekmans et al., 2006). In turn, these clinically observable phenotypes are assumed to be one extreme of a spectrum of sub-clinical disordered ovarian morphology associated with PCO. Indeed, on ultrasound examination, as noted above, a remarkably high 20–30% of women in developed countries (Balen and Michelmore, 2002) and up to 52% of South Asian immigrants to Britain had PCO (Rodin et al., 1998).

In PCOS, excess androgens are linked to increases in the pulse frequency and amplitude of luteinising hormone (LH) secretion and arrest of follicle-stimulating hormone (FSH) levels in the mid-follicular range. The primary anomaly in PCOS is either in the central hypothalamic axis, involving increased LH secretion, overproduction of androgens in either ovary or adrenal, or insulin resistance and hyperinsulinaemia (Sam and Dunaif, 2003).

A remarkable 20–40% of women with PCOS have evidence of insulin resistance, independently of total body fat, and have an associated three-fold risk of developing T2D (Wild et al., 2000). The cellular and molecular mechanisms of insulin resistance in PCOS are characterized by decreased sensitivity to insulin in peripheral tissues, especially muscle and adipose tissue (Sam and Dunaif, 2003), and concomitant abnormalities of pancreatic β cell function (Dunaif and Finegood, 1996). There is a close alignment of the clinical features of PCOS to the constellation of major risk factors for cardiovascular disease—insulin resistance, hypertension, dyslipidemia and visceral adiposity (Sam and Dunaif, 2003), grouped as the MetS.

Genetics of PCOS, the Metabolic Syndrome, and Type 2 diabetes

In 1918, Fisher pointed out that variation of continuous or quantitative traits could be explained by the combined action of a set of individual genes (Fisher, 1918). Common diseases such as PCOS and T2D are also likely to be a combination of common genetic variants (Bougneres, 2002).

In humans, T2D and insulin resistance have a genetic component, and the search for candidate genes has included those involved in obesity, insulin signaling pathways, mitochondrial genes and steroidogenesis (Prentice, 2005). Recent genome-wide scans have confirmed 11 genomic regions, which alter the risk of T2D in European populations (Frayling, 2007). Similarly, for PCOS, genes involved in androgen biosynthesis and secretion, gonadotrophin secretion, the secretion and action of insulin and folliculogenesis are implicated (Urbanek, 2007).

Women with PCOS have a three- to five-fold increase in risk of having a family history of T2D; and conversely 80% of women with T2D, in one report, have evidence of polycystic ovaries (Conn et al., 2000). PCOS and T2D may therefore be different clinical manifestations of an underlying genotypic propensity for pancreatic β cell dysfunction, with phenotypic differences reflecting the presence or absence of coincidental genetic variants at the level of the ovary or in genes controlling insulin resistance, respectively.

The cardinal features of the MetS (or Syndrome X) —insulin resistance, hypertension, dyslipidemia and visceral adiposity—co-exist with reproductive abnormalities in pre-menopausal women with sufficient frequency for this grouping to have been christened Syndrome XX (Sam and Dunaif, 2003). There is high clustering of the phenotypic components of MetS in families and in twin studies, although the search for common genetic factors has been hindered by the lack of an agreed clinical definition (Joy et al., 2008).

Energy balance and PCOS

PCOS occurs in both lean and obese women but, importantly, lean women with PCOS tend to have an abdominal

body fat distribution (Barber et al., 2006). Weight loss and/or physical activity in obese women with PCOS reduces insulin resistance and improves ovulation, menstrual regularity and fertility; conversely, all four worsen with weight gain. Barber et al. (Barber et al., 2006) have highlighted three interrelated features of the link between the PCOS phenotype and obesity: insulin resistance and hyperinsulinaemia, increased ovarian and adrenal androgens impeding ovarian folliculogenesis and an android body fat distribution. In obese women these phenotypic features tend to reinforce each other: for example, increased insulin stimulates androgenic steroid production by the ovaries and these predispose to an android fat distribution, which in turn increases insulin resistance (Barber et al., 2006).

PCOS has not been well studied in populations in which caloric intake and BMI are low. One recent study (Ram et al., 2005) of lean Indian women (BMI < 20) with and without PCOS suggests how the altered metabolism of PCOS could enhance fertility under conditions of chronic energy deficiency. Lean women with PCOS had a sevenfold increase in mean serum leptin (15.5 μg/l), increased insulin and triglycerides, and increased abdominal and triceps skin fold thickness compared to weight-matched non-PCOS controls. Mean serum leptin levels in these lean controls (2.46 μg/l) was close to the suggested critical threshold needed to sustain ovulatory menstrual cycles (Chan and Mantzoros, 2006). An important related observation is that women with anorexia who maintain menstruation have higher mean percent body fat, body fat mass, truncal fat levels and mean leptin and insulin levels than amenorrhoeic anorexic women with a similar body mass index (Dei et al., 2008; Miller et al., 2004). In contrast, other studies show that normal and overweight women with PCOS have similar leptin levels to their weight-matched controls (Caro, 1997).

These data are crucial to our argument, as they suggest that the relationship between BMI and infertility seen in the Nurses Health study and shown in Figure 3 is shifted to the left in PCOS. That is, while women with PCOS will be at greater risk of infertility if overweight, they will actually be more fertile if underweight. The impact of such a shift in a hypothetical lean population with a mean BMI of 19 is shown in Figure 4a. If the PCOS phenotype is assumed to be a manifestation of the Fertility First genotype then this graph can also be interpreted as evidence of an upward shift in the minimum weight optimal for ovulatory fertility in a non-PCOS or insulin sensitive population.

A schematic representation of how improved nutrition might change fertility advantage to disadvantage in women with PCOS is shown in Figure 4b. An upwards shift in the weight distribution of the population would first decrease the prevalence of infertility related to undernutrition, and then increase the prevalence of obesity/PCOS-related infertility.

MECHANISM AND DYNAMICS OF SELECTION FOR THE FERTILITY FIRST GENOTYPE

We contend that the three common conditions—PCOS, T2D, and MetS—represent a persistence of the Fertility First genotype. We now propose mechanisms, which could sustain this genotype in human populations, and suggest dynamic factors, which may account for the epidemiology and geography of these conditions (particularly of T2D, which is better defined and studied). This exploration has been framed by three epidemiologic observations (Diamond, 2003):

1. These genetically based conditions, each strongly associated with insulin resistance in muscle and pancreatic β cell function, are up to 50,000 times more common than would be expected in well mixed and ancient populations by recurrent mutation alone (Diamond, 2003).
2. There is a clear hierarchy of susceptibility to T2D in human populations when they are exposed to energy dense diets high in refined carbohydrates and sugars. Peoples who in the recent past had been foragers, such as Amerindians, Australian Aborigines, and Polynesians, have the highest prevalence, followed by subsistence horticulturalists who have recently undergone or are in the process of economic and demographic transition, followed by Europids who have the lowest prevalence—approximately one half that found in the highest prevalence groups (Diamond, 2003; McMichael, 2001).
3. All of these conditions increase in prevalence as the average weight of a population increases.

Mechanisms of selection

Insulin resistance and reproductive success in times of hunger. We have described a mechanism whereby the PCOS phenotype—an expression of the underlying Fertility First genotype—could confer a fertility advantage under conditions of chronic energy insufficiency. Two mechanisms are suggested:

Insulin resistance could serve to sustain ovulation by diverting available glucose to the preservation of ovulatory function.

Early androgenization, perhaps driven by hyperinsulinaemia secondary to insulin resistance, causes preferential deposition of abdominal fat, thereby sustaining leptin secretion.

When food supply becomes adequate, ovarian fecundity and fertility would first increase as infertility due to under-nutrition declined, thereby diminishing the fertility selection advantage of the Fertility First genotype. With further increases in calorie intake and increasing body weight, that selection advantage would decline further due to the increasing prevalence of PCOS and ovarian infertility (see Fig. 5).

Fertility first in the agrarian period. A corollary of the postulated "left shift" in the ovarian infertility/BMI curve shown in Figure 4 is that insulin sensitivity in a population, which we propose is one of the hallmarks of the agrarian adaptation, involved a raising of the lower bound of body weight optimal for human reproduction.

Insulin sensitivity, by facilitating intracellular uptake of metabolic fuel for normal cell function and thereby improving thermoregulation and resistance to infection (Prentice, 2005) may also, in a catastrophic famine, confer a fertility advantage by investment in somatic maintenance and maternal survival (Shanley and Kirkwood, 2000), delaying reproduction until food availability improves and a successful pregnancy is more likely. This concept of a genetically based trade-off between

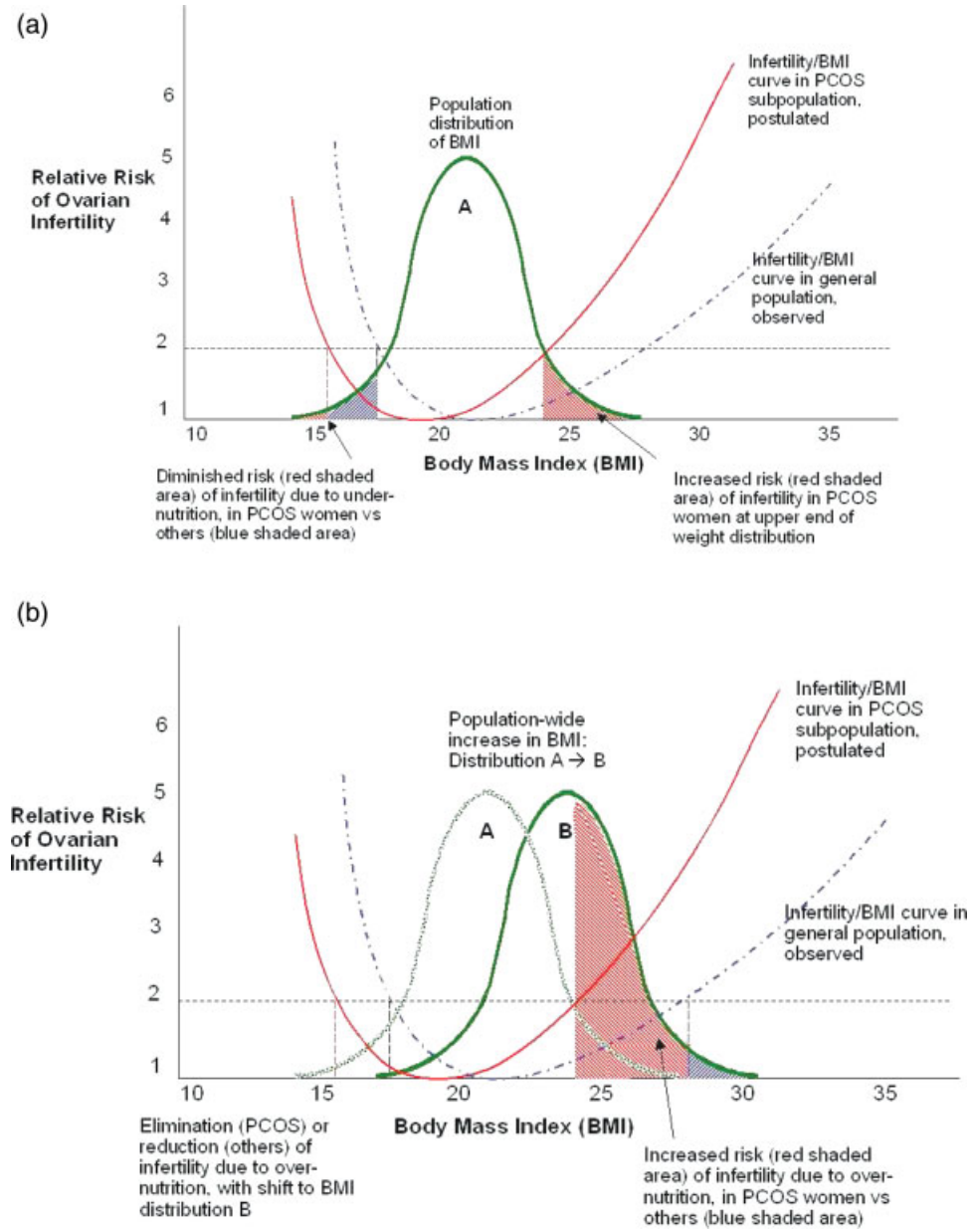

Fig. 4. (a) Postulated left shift in Ovarian Infertility curve in PCOS, with diminished risk of under-nutrition related infertility in PCOS. (b) Changes in ovarian infertility risk profile due to population-wide increases in the distribution of BMI—i.e. distribution A shifts to right to become distribution B. This shift reduces infertility due to low BMI and increases infertility due to high BMI, the latter more so in PCOS.

investment of metabolic resources in growth and reproduction has a resonance with the Disposable Soma Theory of Health and Ageing (Holliday, 1989; Shanley and Kirkwood, 2000). The later life sequelae of both insulin resistance and PCOS—T2D and increased cardiovascular disease risk—could then be viewed as the life-shortening consequences of this disinvestment in soma to sustain reproduction.

Fertility selection. Darwinian evolution through natural selection has two components, fertility and viability selection. That is, genes can confer fertility or survival advantages, respectively. RA Fisher, (Fisher, 1930) summarized the power of fertility selection:

The intensity of selection by differences in fertility .... is sufficient to produce considerable evolutionary changes in relatively short historical periods ... the selective advantage produced by variations (of by no means exceptional magnitude) in innate fertility amounts to over 95% in each generation (Fisher, 1930).

The potential intensity of fertility selection rises as the average number of children falls, (Crow, 1958) and twin studies point to an increased genetic component to

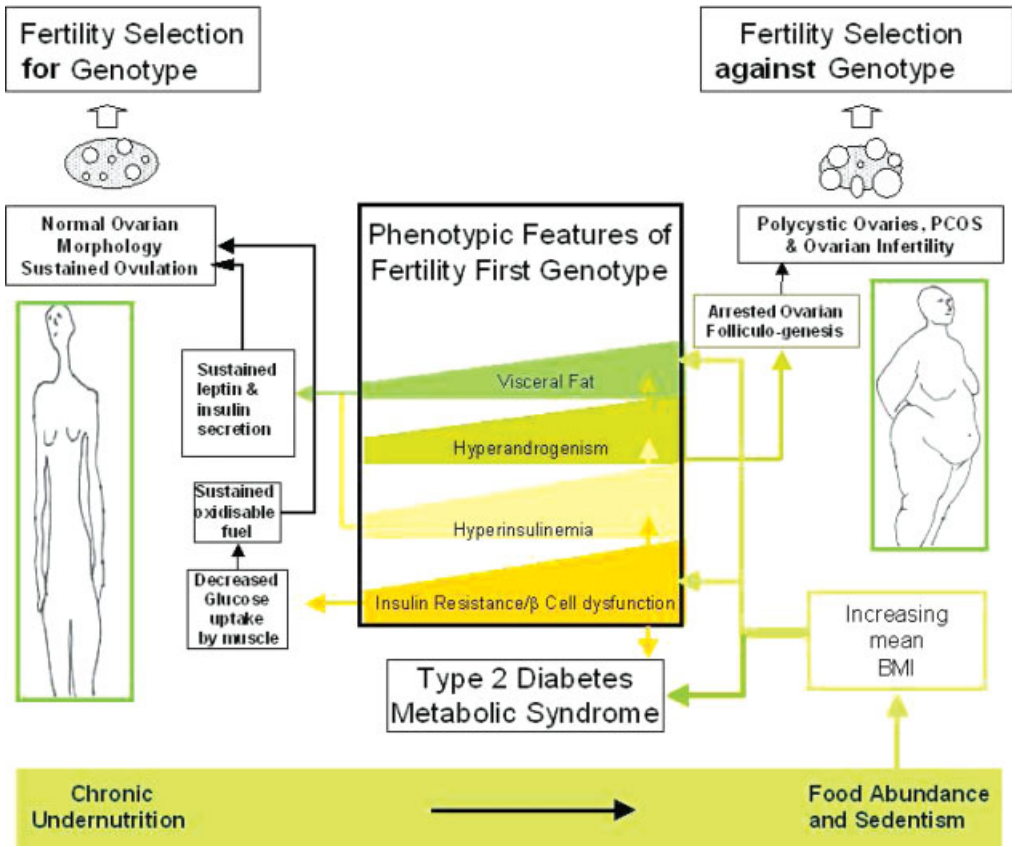

Fig. 5. Reversal of the direction of selection for Fertility First Genotype under changing energetic conditions. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

fertility during periods of fertility transition (Kohler et al., 1999). There is evidence in animals (Renold et al., 1972) and humans on the Pacific island of Nauru (Dowse et al., 1991) that fertility selection may influence diabetes prevalence in a population.

Diamond (2003) has proposed that the relatively lower susceptibility of modern Europid populations to T2D is linked to the attainment of permanent food security in the eighteenth century and that an increased prevalence of obesity caused selective premature mortality of persons with genetic predisposition to insulin resistance and diabetes, and, he hinted, selectively diminished fertility in people with this metabolic profile.

Dramatic environmental change can lead to rapid genetic adaptation, but an apparent halving (Diamond, 2003) of the diabetes gene frequency in 200 years would require a selection advantage of a magnitude [>15% per generation (Cavalli-Sforza and Bodmer, 1971)] probably only achievable with fertility selection in this time period, especially as mortality from T2D-related risks tends to occur after menopause.

Dynamics of selection

Proximity of a foraging past. In modern populations, the nearness of a foraging or early agricultural past would be a determinant of the population prevalence of these Fertility First genes. Pima Indians, for example, have some of the highest rates of T2D seen in any population, including other American Indian groups such as Apache or Navajo. The Pimas are descended from Paleoindians, who were dependent until more recently than other American Indians on bison and other large herbivores as their main food source (Wendorf and Goldfine, 1991).

Fertility and the transition to agriculture. The transition to agriculture saw the average rate of population growth increase from ~1.6 to 4.6 per 100,000 per annum (Coale, 1986). This increase occurred despite the apparently poorer diet and health, and higher levels of child mortality, and as we have argued, nutritionally based seasonality in fecundity, of early agriculturalists (Armelagos et al., 1991). There is a strong case that this population increase was achieved by increased fertility; the availability of weaning foods and their effects on lactational practices are likely to have been particularly important in reducing interbirth intervals (Bentley et al., 2001). In terms of the current hypothesis, these conditions would suggest that in agrarian societies there would be sustained selection pressure to maintain the Fertility First genotype.

Variations in fertility and selection in preindustrial populations. In 1961, the French demographer Henry (1961) defined natural fertility, as opposed to controlled fertility,

as fertility not consciously limited by the number of children born. The distinction was made in terms of parity progression ratios—the proportion of women with N children who go on to have $N + 1$. When applied only to births within marriage it provided a means to compare the physiological variation in human fecundity, stripped of the overlay of societal influences and individual choice (Ellison, 2001). When this measure was used to measure fertility in human populations, wide variations were observed, both within and between countries.

For example, marked differences were observed in marital fertility, but not gross reproductive rate, between European and Asian populations. The former had relatively high marital fertility but a high proportion of women either delaying or never marrying. In East Asia almost all women marry but have much lower marital fertility. Poorer nutrition is likely to have been an important proximate factor in the lower Asian natural fertility (Clarke, 2008).

This is one, albeit important example of how systematic differences in the Malthusian equilibria struck between income and food intake, and fertility and mortality, could create different selection pressures for and against the putative Fertility First genotype.

From hunger to obesity. Between 1700 and 1850, daily caloric consumption increased from 1,600 to 2,400 in France and from 2,100 to 2,300 in Great Britain. Food quality improved more slowly with the share of calories from animal foods increasing from 20 to 25% in England but remaining at 20% in France over this period (Fogel, 2004). These improvements in nutrition occurred in parallel with increases in stature and body weight. The height of military recruits in France between 1700 and 1867 and in England between 1790 and 1878 increased 7 cm. BMI increased accordingly from 18 to 21 and from 21 to 22 in France and England, respectively, over the same periods (Fogel, 2004). Changes of similar magnitude can be assumed to have occurred in women. For many human populations in the twentieth century changes of this magnitude were compressed into much shorter time periods—50 years or less—have been rapidly followed by steep increases in obesity. By the mechanism we have described the gradual reduction in under-nutrition related infertility and rapid increases in average BMI would accelerate selection pressure against the Fertility First genotype over this period.

Fertility transition. Marital fertility began to decline in Europe between 1890 and 1920, broadly coinciding with population wide improvements in nutrition. By 2003, 60 countries with 43% of the world's population have fertility at or below the replacement level of 2.1 children per woman (Lee, 2003). The pace of fertility decline is influenced by the perceived costs and value of children (Lee, 2003), life expectancy and literacy, and other complex cultural factors (Caldwell, 1999).

There is, however, no satisfactory full account of fertility transition, that combines the contributions of demography, anthropology and evolutionary biology (Borgerhoff Mulder, 1998). The evolutionary hypothesis outlined here provides, firstly, a plausible biologic basis for fertility decline: rapid increases in calorie intake and obesity in a population highly selected for the Fertility First genotype could lower average fecundity. Secondly, fertility decline caused by abrupt changes in controlled fertility, such as occurred in the immediate aftermath of the French Revolution (Weir, 1984) could increase the intensity of fertility selection (Crow, 1958). A biological explanation of fertility decline does not of course exclude other causes, and fertility, so profoundly affected by behavior, culture and choice, is determined by an interplay between genetic, biological, cultural, economic and demographic factors.

DISCUSSION

Our investigation of the evolutionary paradox of the PCOS provides, we contend, new insights into the origins and fate of the modern epidemics of diabetes and cardiovascular disease in contemporary human populations. It stands in contrast to the early but still influential thrifty gene hypothesis (Neel, 1962), which postulated that the high prevalence of diabetes in certain human populations was the detrimental legacy of a "thrifty" genotype that enhanced survival during famines among our preagricultural ancestors. Neel (1982) himself revised his hypothesis in the light of the distinction made between Type 1 (childhood onset) and T2D and the growing realization that resistance to insulin action was a defining feature of T2D. There are, in our view, at least three compelling critiques of this hypothesis:

The evidence that insulin resistance itself increases either energy storage (as fat) or energy efficiency is inconsistent, perhaps because the associated hyperinsulinaemia can both increase fat storage and cause central (hypothalamic) suppression of appetite (Porte, 2006). Evidence from longitudinal studies in adult Pima Indians (Swinburn et al., 1991) Caucasians, Mexican Americans, Creoles, Chinese, Asian Indians (Hodge et al., 1996) and in pregnant women (Catalano, 1999) suggest that the most insulin-sensitive (the least insulin-resistant) individuals and those with low insulin levels may have the greater potential for weight gain.

The levels of fat storage in contemporary hunter-gatherer and subsistence agriculture populations are low with average body mass indices in these populations in the 18–22 range (Speakman, 2007).

The underpinning assumption of periodic starvation among pre-agricultural people—feast or famine—is not corroborated by ethnographic studies of contemporary hunter gatherer populations (Cordain et al., 1999) who had access to a wide range of wild plant and animal foods.

The "thrifty phenotype" hypothesis (Hales and Barker, 1992) poses an alternative developmental and evolutionary explanation for the inter-ethnic differences in diabetes occurrence—an explanation that accounts particularly for the escalating diabetes prevalence in developing countries (Yajnik, 2001). This hypothesis had its origins in observed associations between low birth weight and the subsequent development of T2D, now replicated in many populations. A recent meta-analysis (Whincup et al., 2009) has given form and shape to the magnitude of this relationship. This hypothesis postulates that poor fetal nutrition leads not

only to limited fetal growth but to reduced cell numbers in the endocrine pancreas, and T2D and the MetS in later life (Gluckman and Hanson, 2004; Hales and Barker, 1992). In an evolutionary context this phenomenon may be an appropriate adaptive response to adverse pre-natal nutritional circumstances (Bateson et al., 2004), but it seems unlikely that low birth weight accounts for more than a small proportion of diabetes (Boyko, 2000). It is also difficult for this hypothesis to account fully for the hierarchy of susceptibility to T2D observed in human populations: the generally poorer nutrition of agricultural populations would suggest that they, and not foragers, would be at higher, rather than the observed lower, risk of developing diabetes. This hypothesis is not inconsistent with our own and these processes could occur in parallel.

Both the thrifty genotype and thrifty phenotype hypotheses assume that the improvement in diet and energetic conditions for the human majority since the eighteenth century is too recent to have effected underlying changes in gene prevalence (Di Rienzo, 2006). Our hypothesis addresses this problem directly by proposing that through the mechanism of fertility selection rapid selection against the Fertility First genotype has been responsible for an approximate halving of the prevalence of diabetes in Europids in 200 years. By this process we imply that, as countries develop, the elimination of undernutrition may, by both relaxing selection pressure for and increasing selection pressure against the Fertility First genotype, reduce the vulnerability of those populations to emerging global epidemics of diabetes and cardiovascular disease.

Finally, our hypothesis lends itself to testing and falsification:

- It predicts that young women recovering from anorexia nervosa with a BMI less than 18.5 and with evidence of polycystic ovaries or PCOS should return earlier to menses as weight is gained, compared to counterparts without PCO/PCOS. A recent study (Dei et al., 2008) has confirmed that insulin levels predict an early return to menses in such a group.
- There are established research cohorts of famine survivors in the Netherlands, the Channel Islands, St Petersburg and Bangladesh. Women able to conceive during famines would, we predict, be more likely to develop T2D in later life.
- International surveys can elucidate whether differences in PCOS prevalence mirror those seen for T2D between European and all other populations.

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